REMARKS

The Office Action mailed November 27, 2006, has been carefully reviewed.

Claims 33, 34 and 37 have been amended.

Claims 24 – 32 stand withdrawn as deemed to be allegedly directed to a non-elected invention; claims 1-23, 35, 36, 42 and 47 remain canceled.

Claims 33- 34, 37 – 41, 43-46 and 48 - 52 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement.

Claims 33- 34, 37 – 41, 43-46, 48 – 52, and 53-54 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement.

Claims 33- 34, 37 – 41, 43-46, 48 – 52 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement.

Claims 33- 34, 37 – 40, 43-46, 48, 49, 51, 53, and 54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 34, 37, 46, 48 – 51, 53 - 54 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenta et al. (WO 99/16467) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 33, 49, and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659) in view of Hem et al.

Claims 33, 38, and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659).

Claims 53 and 54 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims as amended herein are fully supported by the application as originally filed. No new matter has been added. Reconsideration and allowance of the present application are respectfully requested in view of the foregoing amendments and the following additional remarks which have addressed all the grounds for objection or rejection or otherwise have rendered them moot.

Claim Rejections under 35 U.S.C. § 112, first paragraph

Claims 33 - 34, 37 – 41, 43-46 and 48 - 52 stand rejected under 35 U.S.C. §112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner asserts that Applicant's recitation that a derivative binds IgE to a lesser extent than the wild type allergen comprises new matter since derivatives are taught as possessing

reduced allergenic activity and allergenic activity is not defined in relation to IgE binding levels.

In order to advance the prosecution of this application, Applicants have amended the claims to recite "allergenic activity" instead of " IgE-binding" thereby obviating this ground for rejection.

Suffice it to add that in its ordinary usage, the terms allergenic activity, allergenicity and IgE-binding or IgE reactivity convey certain definite notions to a skilled artisan in the field and without prejudice or disclaimer, hereby advises the Examiner as follows.

The term "allergenic activity" is taken to mean that an antigen can elicit an allergic reaction in vitro or in vivo upon provocation. Basophils from an already senstized allergy patient can be challenged with the allergen to release mediations, an allergic reaction taking place. In other words, allergenic activity refers to the ability of an antigen to elicit an allergic reaction in an already sensitized person. Allergenicity on the other hand means that a given antigen can induce an allergic immune response in an unsensitized individual to make the person allergic. Applicants admit that IgE binding does not necessarily correlate with allergenic activity. For instance, IgE reactive haptens bind IgE but do not induce crosslinking of mast cells-bound IgE and hence fail to induce the release of biological mediators and as a result, no allergic reaction occurs.

In view of the foregoing, Applicants believe that there is no longer a basis for this ground for rejection and respectfully ask that it be withdrawn.

Claims 33- 34, 37 – 41, 43-46, 48 – 52, and 53-54 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement.

The Examiner asserts that the claim scope is too broad and encompasses IgE-mediated disorder of any causal origin. In response, Applicants have amended the claims to limit them to IgE-mediated disorders resulting from exposure to allergens of alder, hazel and birch.

Regarding whether the specification enables the prevention of IgE-mediated disorders resulting from exposure to allergens of alder, hazel and birch, Applicants submit that the amendment as currently made satisfies the enablement requirement with respect to prevention of allergic disorders of the particular kind claimed. In view of the amendments, Applicants' claims should no longer be construed as preventing IgE-mediated disorders in general, but IgE mediated disorders as a result of exposure to the allergens of alder, hazel and birch. Applicants are troubled by the Examiner's assertion that since prevention cannot be had with

a hundred percent certitude, that the instant invention is not enabled for prevention of IgE-mediated allergic disorder. Applicants respectfully disagree with the Examiner. As is generally understood, treating in the medical arts involves any measure aimed at ameliorating, arresting, or eliminating the symptoms of a disorder. Prevention on the other hand is a measure aimed at avoiding the symptoms of a disorder. Applicants believe that these terms are best and most reasonably construed in the context of allergy symptomatology. Properly construed, it is understood that the derivatives of the instant invention could be used to pre-sensitize an individual desiring to avoid allergy symptoms as a result of subsequent exposure to the natural allergens of hazel, birch and alder. The relevant question is not whether the disease condition is avoided at the molecular level, but whether the disease condition is avoided at the symptomatic level. Applicants believe that prophylactic use of the derivatives of the present invention is adequately enabled.

Regarding whether Bet v 1 trimers do comprise a diminished capacity to bind IgE due to the present of IgE blocking antibodies in vivo; Applicants assert that the therapeutic attribute of the allergen derivatives of the claims as now amended relates to their decreased allergenic activity in relation to the wild-type allergen and the Examiner's contention is moot as a result.

The Examiner further asserts that the specification does not provide adequate guidance and direction to make and use the derivatives of the instant invention but merely invites a skilled artisan to conduct additional research prior to making and using applicant's claimed invention. Applicants respectfully disagree and hereby traverse as follows.

Applicants' invention relates to the generation of candidate immunotherapeutic agents and their use in the treatment or prevention of causally related IgE-mediated allergic disorders. Admitted, some trial and error may be involved but the question is not whether trial and error is involved but whether the nature of the experimentation required to practice the full scope of the invention is undue. Merely because trial and error may be involved does not make the experimentation undue. As the Examiner can appreciate, a single experiment may be more cumbersome, more arduous, more resource intensive and more mentally taxing than a whole series of trial and error experiments. Undue experimentation is thus a relative term and may best be determined by comparative analysis of alternative methodologies designed for the same end.

In that regard, Applicants invite the Examiner to consider what had hitherto been the case in terms of generating candidate immunotherapeutic agents. Typically, a naturally occurring allergen is identified, said allergen is rigorously characterized in terms of its

primary, secondary, tertiary and even quaternary structures; then said allergen is epitopically characterized; then systematically derivatized prior to conducting a whole series of experiments to determine whether the derivation yielded candidate therapeutic agents, followed finally by in vivo validation of the candidate therapeutic agents. Clear, the level of experimentation will be undue in the classic epitopic mapping methodology.

On the other hand, the current invention is most aptly described as heuristic and leads quickly, without under experimentation to the identification of candidate immunotherapeutic agents even though some trial and error might be involved. Unlike the classic methodology, the instant methodology is not so concerned about the structure of the derivative as it concerned that the derivatives are therapeutic candidates. It is the position of the invention that a derivative may be generated by any means known, expedient, and undue, and as such sees no purpose in burdening the specification with what is readily available in a standard biotechnology laboratory manual. It is the position of the invention, however, that it takes a very simple trial to determine whether the derivative is a candidate therapeutic agent and if it is, said derivative may be used as such without ever trying to determine its exact molecular structure. The claims set only two criteria namely: whether the derivative (of whatever structure) induces IgE-blocking antibodies in vivo and has substantially diminished allergenic activity. The claims then go one step further to teach how to use these derivatives (of whatever structure) to treat causally related IgE-mediated allergic disorders.

Indeed, the heuristic methodology of the instant invention is by far less experimentally intensive than the classical method and it is respectfully asserted that though trial may be involved, yet those trials are not patentably undue.

The methodology of the present invention is based on the theory that allergen-specific IgG antibodies, termed blocking antibodies, can antagonize the cascade of allergic inflammation resulting from allergen recognition by IgE antibodies. The instant invention is based on the rationale that blocking antibodies inhibit allergen-induced release of inflammatory mediators from basophils and mast cells as well as IgE-facilitated allergen presentation to T cells, thus leading to suppression of T cell activation. Furthermore, the development of blocking antibodies is associated with reduced boosts of allergen-specific IgE production in patients receiving allergen-specific immunotherapy of the present invention. Thus blocking antibodies have protective activity by inhibiting immediate as well as late inflammatory responses and long-term ameliorating activity on the allergic immune response by antagonizing the underlying IgE production. Induction of blocking antibodies is thus an

important mechanism underlying allergen-specific immunotherapy. See Specification pages 5 and 6.

Since the claims are distinctly drawn to the use of derivatives that induce IgE-blocking antibody production, Applicants ask the Examiner to recognize that their method of treating allergic disorders is an elegant patentable departure from the experimentally intensive methodology of first typifying the epitopic domains of allergens and directing modifications thereto. The instant invention, on the other hand, and especially as now distinctly claimed, concerns itself with treatment using derivatives simply and quite elegantly identified by their ability to elicit IgE-blocking antibody production *in a test animal.* Applicants respectfully ask that this ground for rejection be withdrawn for at least the fact that the screening of candidate immunotherapeutic agents of this invention does not involve undue experimentation.

Claims 33- 34, 37 – 41 , 43-46, and 48-52, stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. The Examiner asserts that the three examples concerning the birch pollen allergen Bet v1 is insufficient to enable claims to the genus – namely derivatives of wild type allergens of alder, hazel and birch. Applicants respectfully disagree. The presented examples are to validate the inventors discovery that IgE-blocking antibodies do present a therapeutic handle for combating IgE-mediated allergic disorders. The Examples are not scope limiting, in the sense that the full scope of the invention can be practiced without undue experimentation. The written description requirement has been met in this case by disclosure of relevant identifying characteristics – namely that the candidate therapeutic agents of this invention are those which upon injection into an immunological model elicit both IgE-blocking antibodies production and also have reduced allergenicity compared to wild-type allergens. This identifying characteristic, without more, has given possession to the Applicants, as at the filing date, of treatment methods using the results of the elegant in vivo screening methodology of the present invention.

In other words, the full scope of the present invention can be attained without knowing the structure of the derivative itself and it is therefore improper to request that the structure of all the derivates encompassed by the claims be disclosed in the specification. As the Examiner can appreciate, a crude allergen extract can be used for therapeutic purposed without knowing the structural make-up of the extract. In that respect, there is no ground for this rejection and it is respectfully requested that it be withdrawn.

Claim Rejections under 35 U.S.C. § 102(b)

Claims 33-34, 37 – 40, 43-46, 48, 49 and 51 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659). The Examiner asserts that Vrtala et al., teach a method of treating allergy by administering derivatives of Bet v1 that induce the production of IgE-blocking antibodies and that are not bound by IgE antibodies that are specific for wildtype Bet v1. Applicants respectfully disagree and now traverse as follows.

A § 102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. *Paperless Accounting, Inc. v. Bay Area Rapid Transist Sys.*, 804 F.2d 659, 231 USPQ 649 (Fed. Cir. 1986), cert. denied, 480 U.S. 933 (1987). Indeed, to anticipate, a publication "must show the same subject matter as that of the patent, and must be identical in all material respects." *Hupp v. Siroflex of America, Inc.*, 122 F.3d 1456, 43 USPQ2d 1887 (Fed. Cir. 1997).

The Vrtala publication is at best a mere experimental disclosure of certain aspects of the present invention and does not enablingly disclose the invention as claimed. Particularly, and as the Examiner correctly observed, the Vrtala reference had not enabled treatment of human IgE-mediated disorder. Claim 33 as amended has been limited to human patients and for that at least, there is no further basis for a § 102(b) rejection and it should therefore be withdrawn.

Additionally, Applicants respectfully ask the Examiner to consider that claim 33 and its dependent claim have a periodicity element which is essential to successful immunotherapy. The Vrtala reference merely administered monthly administration of the allergen derivatives in order to conceptually investigate the subject matter thereof. There was no attempt in the Vrtala reference to investigate optimal periodicity intervals for the allergen administration and although it may have made reference to monthly injection of allergens, the Vrtala reference cannot reasonably be said to have sufficiently disclosed, to a patentably enabling detail, the periodicity element claimed in the invention and which is very vital to a successful immunotherapy. For that at least, there is again no further basis for retaining this § 102(b) rejection and Applicants respectfully ask that it be withdrawn.

Claims 33, 34, 37, 46, 48-51, 53 – 55 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Valenta et al. (WO 99/16467) as evidenced by Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659). Applicants respectfully disagree.

Again, to be anticipating, a prior art reference must disclose "each and every limitation of the claimed invention, ..., must be enabling, and must describe ... the claimed invention sufficiently to have placed it in possession of a person of ordinary skill in the field of the invention." *In re Paulsen*, 30 F.3d 1475, 1478-79, 31 USPQ2d 1671, 1672 (Fed. Cir. 1994).

The Examiner acknowledges that Valenta et al. WO 99/16467 had not disclosed the concept of blocking antibodies but insisted that it is inherent in the disclosure of Vrtala et al. Applicants however believe that neither Valenta et al. alone or in combination with Vrtala et al. can be said to have enablingly disclosed the periodicity element of claim 33 and its dependent claims. For that at least, there is no basis for this ground for rejection and it is respectfully requested that it be withdrawn.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 33, 49, and 50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659) in view of Hem et al.

Applicants respectfully disagree that there is sufficient motivation to make the asserted combination. Hem et al., on page 249 taught that the aluminum containing adjuvants have been used for vaccines like diphtheria vaccine. The present invention has to do with immunotherapeutic agents which is not the same as vaccines.

But assuming the combination can be made, the asserted combination cannot on the basis of the arguments presented above render obvious the claims of the present invention. Basically, the periodicity element of the present invention cannot be met by the asserted combination. Again, although Vrtala mentioned monthly injection of allergen derivatives, it had not sufficiently disclosed to one of skill in the art the periodicity of injections so critical to successful immunotherapy. Basically Vrtala taught a concept but had not reduced it to practice and the concept taught by Vrtala did not render the periodicity element of the present invention obvious by any stretch.

For that at least, there is no basis for this rejection and Applicants respectfully ask that it be withdrawn.

Claims 33, 38, and 41 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Vrtala et al. (J. Immunol., December 1, 2000, 165:6653-6659). The Examiner's basis for this rejection is that determining the optimum or workable ranges in terms of time intervals

between administrations of allergens involves only routine skill in the art. Applicants respectfully disagree.

Applicants understand that a simple and elegant screening procedure of this invention involves routine skill in the art and that is why Applicants believe that there are in possession of fragments of allergens which meets the two prong limitation of claim 33. But the Examiner may not avail himself of hindsight gained by reviewing the instant Application in order to mount objections and/or rejections thereto. Allergy vaccines may be administered once in a life time, once in a season, and so on, but there is nothing obvious about determining not only the relevant periodicity of administration but the exact dosages involved. All of that information are garnered through rigorous experimentation that warrant protection for the ingenuity in discovering first how to screen allergen derivatives as potential immunotherpaeutic agents, then how to administer those allergen derivatives to treat IgE mediated disorders; both the screening and the administration warranting patentable protection for their immense contribution to the advancement of the science of immunotherapy.

CONCLUSION

In view of the foregoing remarks, Applicants submit that there is no basis for applying the previous rejection to the pending claims and withdrawal of the rejections is respectfully requested. The claims are believed to be in condition for allowance, and Applicant earnestly solicits from the Examiner early notification of allowability.

Should the Examiner have any questions or believe a personal or telephonic interview may be in order, she is invited to contact the undersigned at his earliest convenience.

Respectfully submitted,

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